

IN THE CLAIMS

Please amend the claims as follows:

Claim 1 (Currently Amended): ~~Method~~ A method for evolving a protein X so as to modify its characteristics comprising the following stages:

- a) obtaining mutants X* from the sequence coding for the protein X by random mutagenesis;
- b) ~~transformation of~~ transforming cells comprising a phenotype [P-] with vectors comprising the mutated nucleic acids obtained in stage a) coding for the proteins X*, P- signifying that said cells are auxotrophic for the substance P,
P being the product of the action of X on its natural substrate S;
- c) ~~culture of~~ culturing said cells in a medium comprising a substrate S*, S* being an analogue of the natural substrate S of protein X; and
- d) ~~selection of~~ selecting the cells [P-:: X*] which have survived stage c) in which the proteins X* are capable of carrying out the biosynthesis of the product P from the substrate S.

Claim 2 (Currently Amended): The method ~~Method~~ according to claim 1, characterized in that the mutant protein X* obtained is a protein having an activity similar to the natural protein X, X* and X belonging to common or neighbouring enzyme classes having at least the first three figures of the 4-figure EC international nomenclature classes.

Claim 3 (Currently Amended): The method ~~Method~~ according to claim 1 ~~one of claims 1 and 2~~, characterized in that the cells used in stage b) are obtained by inactivation of at least one gene involved in the natural metabolic pathway leading to product P.

Claim 4 (Currently Amended): The method ~~Method~~ according to claim 3, characterized in that the protein X* complements the deficiency of the natural metabolic pathway leading to product P in a medium provided with substrate S*.

Claim 5 (Currently Amended): The method ~~Method~~ according to claim 1 ~~one of claims 1 to 4~~, characterized in that the activity of protein X on substrate S is at least 2 times greater than its activity on substrate S*.

Claim 6 (Currently Amended): The method ~~Method~~ according to claim 1 ~~one of claims 1 to 5~~, characterized in that the activity of protein X* on substrate S* is at least 10 times greater than its activity on substrate S.

Claim 7 (Currently Amended): The method ~~Method~~ according to claim 1 ~~one of claims 1 to 6~~, characterized in that protein X is selected from the ribosyltransferases belonging to the EC classes 2.4.2. ~~—, in particular the N-deoxyribosyltransferases of EC class 2.4.2.6.~~

Claim 8 (Currently Amended): The method ~~Method~~ according to claim 1 ~~one of claims 1 to 6~~, characterized in that the random mutagenesis of stage a) is carried out either by variation of the manganese concentration during the PCR reaction, or by use of promutagenic nucleotide analogues or ~~also~~ by the use of primers comprising a random sequence.

Claim 9 (Currently Amended): ~~The method Method~~ according to claim 1 ~~one of~~
~~claims 1 to 8~~, characterized in that said cells are procaryotic or eucaryotic cells, ~~preferably E.~~
~~coli.~~

Claim 10 (Currently Amended): ~~A method Method~~ according to ~~one of claims 1 to 9~~
for evolving an N-deoxyribosyltransferase (DTP) so as to obtain an N-
dideoxyribosyltransferase characterized in that it comprises the following stages:

- a) obtaining DTP* mutants with the sequence coding for an N-
deoxyribosyltransferase (DTP) by random mutagenesis;
- b) ~~transformation of~~ transforming cells comprising an [N-] phenotype with vectors
comprising the mutated nucleic acids obtained in stage a) coding for the DTP* proteins, N-
signifying that said cells are auxotrophic for at least one nucleoside, said nucleoside being the
product of the action of DTP on its natural substrate dR-N;
- c) ~~culture of~~ culturing said cells in a medium comprising a substrate ddR-N; and
- d) ~~selection of~~ selecting the [N-:: DTP*] cells which have survived stage c) in which
the DTP* proteins are capable of carrying out the transfer of the dideoxyribose (ddR) from a
dideoxyribonucleoside to another nucleoside leading to the production of the N nucleoside
necessary for the survival of the cells.

Claim 11 (Currently Amended): ~~Method~~ The method according to claim 10
characterized in that the N-deoxyribosyltransferase (DTP) is the DTP of *Lactobacillus*
leichmannii of SEQ ID No1.

Claim 12 (Currently Amended): ~~Method~~ The method according to ~~one of claims 10 and 11~~ claim 10, characterized in that the cells used in stage b) are Δ pyrC, Δ cod A, Δ cdd *E.coli* bacteria deficient in the metabolic pathway leading to uracil.

Claim 13 (Currently Amended): A mutated ~~Mutated~~ protein X* ~~capable of being~~ obtained by the method of claim 1 ~~according to one of claims 1 to 12~~, characterized in ~~that it~~ that the mutated protein has comprises a modified activity relative to the initial protein X.

Claim 14 (Currently Amended): A mutated ~~Mutated~~ N-deoxyribosyltransferase ~~capable of being~~ obtained by the method of claim 10 ~~according to one of claims 1 to 12~~, characterized in that it ~~has~~ comprises an N-dideoxyribosyltransferase activity, ~~activity and/or~~ an activity on deoxy or dideoxyribonucleoside analogues comprising a modified base, or a combination thereof.

Claim 15 (Currently Amended): ~~Mutated~~ The mutated N-deoxyribosyltransferase according to claim 14 characterized in that it comprises the sequence SEQ ID No 2 comprising the mutation G9S and in that it ~~has~~ comprises an N-dideoxyribosyltransferase activity.

Claim 16 (Currently Amended): A nucleic ~~Nucleic~~ acid comprising a sequence coding for N-dideoxyribosyltransferase according to claim 15, ~~in particular the sequence SEQ ID No 3.~~

Claim 17 (Currently Amended): ~~Expression~~ An expression vector comprising a coding sequence according to claim 16.

Claim 18 (Currently Amended): ~~Vector~~ The vector according to claim 17, characterized in that said coding sequence is fused to an effective promoter in eukaryotic cells, and/or procaryotic cells, or a combination thereof.

Claim 19 (Currently Amended): ~~Vector~~ The vector according to claim 17 ~~one of~~ claims 17 and 18, characterized in that it is a plasmid capable of transforming and remaining in *E. coli*.

Claim 20 (Currently Amended): ~~Host~~ A host cell comprising a vector according to ~~one of claims 17 to 19~~ claim 17.

Claim 21 (Currently Amended): A method of transferring a dideoxyribose (ddR) from a dideoxyribonucleoside to another nucleoside comprising
transferring the dideoxyribose from the dideoxyribonucleoside to another nucleoside
with the Use of an N-dideoxyribosyltransferase of claim 14 according to one of claims 14 and
~~15 for the transfer of a dideoxyribose (ddR) from a dideoxyribonucleoside to another~~
nucleoside.

Claim 22 (Currently Amended): ~~Use according to claim 21 for the preparation of A~~
nucleoside or nucleotide analogues analog having comprising anti-tumorous properties
prepared by the method of claim 21.

Claim 23 (Currently Amended): A method of preparing ddl or ddC comprising preparing the ddl or the ddC according to the method of claim 21 ~~Use according to claim 21 for the preparation of ddl or ddC.~~

Claim 24 (Currently Amended): ~~Method~~ A method for the preparation of compounds comprising a stage ~~consisting of~~ comprising
preparing the compound with the utilizing a mutated protein of claim 13 according to one of claims 13 to 15.

Claim 25 (Currently Amended): Nucleoside or nucleotide analogs prepared by the method of Claim 24 ~~Method according to claim 24 for the preparation of nucleoside or nucleotide analogues useful for the treatment of cancer or infectious diseases, in particular dideoxynucleosides, in particular ddC and ddl.~~

Claim 26 (Original): PAK 9 strain of *E. coli* of genotype Δ pyrC::Gm, Δ codA::Km, cdd::Tn10 deposited at the CNCM under accession number 1-2902.